

**UNITED STATES DEPARTMENT OF COMMERCE****Patent and Trademark Office**Address: COMMISSIONER OF PATENTS AND TRADEMARKS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/171,854 10/22/98 JOOS

S 3528.38.US00

HM12/0324

EXAMINER

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ART UNIT	PAPER NUMBER
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1655

DATE MAILED:

03/24/00 6

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/171,854	Applicant(s) Stefan Joos et al.
	Examiner Bradley L. Sisson	Group Art Unit 1655

Responsive to communication(s) filed on _____

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle* 1035 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

Claim(s) 1-8 _____ is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 1-8 _____ is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

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DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Group 1650, Art Unit 1655, and has been assigned to Primary Examiner Bradley L. Sisson.

Drawings

2. The drawings are objected to for reasons as stated on FORM PTO-948 (Rev. 8-98). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

Sequence Rules Compliance

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is requested to return a copy of the attached Notice to Comply with the reply.

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Specification

4. The disclosure is objected to because of the following informalities: The first paragraph of the specification needs to reflect any claim for benefit of priority.

Appropriate correction is required.

5. The use of the trademark TWEEN 20 has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

6. The attempt to incorporate subject matter into this application by reference to "Kallionemi *et al.*, *Science* 258:818, 1992; Kallionieme O. -P., *et al.*, *Genes Chromosome Cancer*, 10:231, 1994, and Lichter P., *et al.*, in *Human Chromosomes*, eds. Verma R.S. and Babu A., New Zyork, 1995, p. 191" at page 3 of the specification is improper because the cited prior art discloses the methods and means by which comparative genomic hybridization is performed.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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8. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Pages 2-3 of the specification disclose that the identification of any change in copy number of a target sequence is achieved via performing comparative genomic hybridization. As indicated *supra*, the specification does not enable this form of detection as essential subject matter has been improperly incorporated by reference. The specification does not enable any alternative means by which one simple (i) amplifies nucleic acid in a cell used as a base line or standard; (ii) using the now amplified DNA in an *in situ* hybridization reaction and then subject all of the nucleic acid to further amplification; and (iii) to then, without further manipulation, be able to identify “numerical changes in the amplified DNA.”

The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

“ ‘[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.’ *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) (‘[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.’).

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"Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

"It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

9. The claimed invention related directly to the performance of hybridization reactions and as such, the claimed invention is sensitive to the conditions employed in such a reaction. As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

1. The purity of the nucleic acid preparation.
2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.

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3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.

4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25° - 30° C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and

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increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 C, will, with increasing effectiveness, remove non-fully complementary hybridization products. Neither the written description nor the specification address how these issues are addressed such that a reproducible method can be readily practiced by a skilled artisan less said artisan resorts to undue experimentation. For the above reasons, and in the absence of convincing evidence et the contrary, the claimed invention has not been found to be enabled by the specification as filed.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite with respect to just what constitutes "numerical changes" and "tag primers." Claims 2-8, which depend from claim 1, fail to overcome these issues and are similarly rejected.

12. The term "small cell population" in claim 4 is a relative term which renders the claim indefinite. The term "small cell population" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

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13. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Those steps and means by which a comparison can be performed such that a "Numerical change" can be detected and evaluated. The specification teaches performing such steps by comparative genomic hybridization (claim 6), however, just what steps are involved in such a method are not recited.

Claim 8 is confusing with respect to just how the primers relate to the amplified DNA. Seemingly, the primers are flanking the amplified sequence which would not have the primers as part of the amplified sequence but rather, have the primers hybridized to the amplified sequence. However, the very nature of amplifying the sequences speaks to the use of primers which would be incorporated into the amplified sequence and in essence are part of the amplified sequence. Clarification as to the placement, orientation of the primers is requested.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. from 5 p.m. to Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-7230.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

B. L. Sisson

BRADLEY L. SISSON
PRIMARY EXAMINER
GROUP 1800 1650

3/16/00

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

1. This application clearly fails to comply with the requirements of 37 CFR 1.821-1.825. Applicant's attention is directed to these regulations, published at 114.00 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

7. Other: _____

Applicant must provide:

An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

A statement that the content of the paper and computer readable copies are the same, and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact

For Rules Interpretation, call (703) 308-1123

For CRF submission help, call (703) 308-4212

For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.